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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,033	04/24/2006	Wolfgang Stahle	24945-0031	9140

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,033	STAHLE ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 7/25/2007 is acknowledged. The traversal is on the ground(s) that searching the full scope of claim 1 does not constitute a search burden. This is not found persuasive because when all of the possibilities of variables L (10 groups) and E, G, M, Q, and U (either C or N) are considered, there are (10 x 4) possibilities for the core of the molecule. In addition, the point of attachment for variable L is anywhere on the phenyl ring.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

Complete revision of the content of the abstract is required on a separate sheet.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. In the claimed compounds, the benzimidazole is one-third of the molecule. There are other parts to the molecule, including a benzene ring and a pyridine ring.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-14 and 17-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for parent compounds of compound 1, does not reasonably provide enablement for all pharmaceutically useful derivatives and solvates of the compounds of claims 1 and 9, and complex compositions involving compounds of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants are enabled for the preparation of compounds of claim 1 where variables E, G, Q, U, and M combine to form a pyridine ring. This synthesis is shown on pages 70-73 of the specification. Applicants do not show composition of two or more active ingredients in which any compound of claim1 is involved. Applicants only show pharmaceutical formulations where a compound of claim 1 is formulated into a pharmaceutically acceptable form (pages 77-79). In each of these formulations, the only active ingredient is a compound of claim 1. Applicants do not show any examples where an additional compound cited in claims 27-29 (although examples of each agent are listed in the specification on pages 61-64), and therefore it is difficult to determine if these compositions are actually viable. What is the ratio of active ingredients to one another? Do all of the possible combinations work? Do some combinations have adverse side effects, making them dangerous?

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the

amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds of claim 1 where variables E, G, Q, U, and M form a pyridine ring. Thus, the claims taken together with the specification imply compounds of claim 1 can inhibit TIE-2 kinase, and consequently treat disorders that are caused by neovascularization.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Compounds of the elected group are considered novel. However, the formation of solvates is unpredictable. Vippagunta (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26) states on page 18, under heading 3.4, "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent." Applicants do not show preparation of any pharmaceutically useful derivatives of the parent compound, but only show preparation of the parent compound.

(5) The relative skill of those in the art:

One skilled in the art is familiar with the preparation of compounds of claim 1.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of the parent compounds of the elected group.

However, the specification does not provide guidance for the preparation of solvates and "derivatives" of the elected group. No compositions of at least two active ingredients were prepared by applicants, and therefore it is hard to determine of compositions claimed in claims 27-29 are possible.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-14 and 17-36 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. Claims 12-13 and 17-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of TIE-2 kinases, treatment of the specific cancers cited in claims 17-19, and treatment of ocular diseases associated with neovascularization, does not reasonably provide enablement for treatment of diseases caused by RAF Kinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants show that only compound of the elected group can effectively inhibit TIE-2 kinase (page 77). Applicants sufficiently correlate the modulation of TIE-2 to the treatment of the different cancers cited in claims 17-19 and ocular diseases associated with neovascularization. However, applicants do not show that any compounds of claim 1 can modulate RAF kinases. Applicants also state that RAF kinases are serine or threonine kinases (page 8, line 4), and since applicants only show that the elected group inhibit tyrosine kinases (TIE-2 is a tyrosine kinase), treatment of diseases caused by RAF kinases is not enabled.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds of claim 1 and various methods of using the compounds. Thus, the claims taken together with the specification imply compounds of claim 1 can treat diseases caused by TIE-2 kinase.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

TIE-2 kinase is known as a primary factor in abnormal cell growth, and therefore modulation of this enzyme can treat the different cancers cited in claims 17-19 and ocular diseases associated with neovasularization. Campochiaro (*Expert Opinion in Biological Therapy*, **2004**, *4(9)*, 1395-1402) states that Tie-2 receptor modulates the signalling in the vascular endothelial growth factor (VEGF) pathway (see abstract). Based on the reasoning of Campochiaro, modulation of TIE-2 can only treat ocular disease where neovascularization occurs, not all ocular diseases.

(5) The relative skill of those in the art:

One of ordinary skill in the art is familiar with testing of compounds and their ability to inhibit enzyme activity.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for inhibition of TIE-2 by the elected group and therapeutic use for different cancers and ocular diseases in which neovascularization occurs.

However, the specification does not provide support that the elected compounds can inhibit RAF kinases.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to 12-13 and 17-36 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "at least 1 compound of claim 1" is vague. How many compounds of claim 1 are being used in the composition? The composition may have an unlimited amount of compounds of claim 1.

Claim Objections

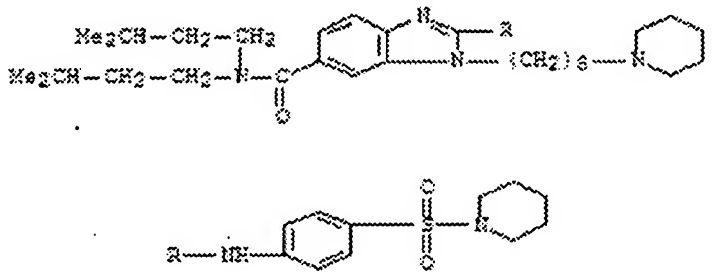
9. Claims 1 and 9 are objected to because of the following informalities: they contain non-elected subject matter. Appropriate correction is required.

Allowable Subject Matter

10. The elected species is considered novel.

11. The following is a statement of reasons for the indication of allowable subject matter: the closest prior art of record belongs to Poitout et al. (FR 2851563, issued August 27, 2004, see HCAPlus abstract). Poitout et al. report the structure shown below, which does not read on the elected group because a piperidine ring cannot be a ring formed by variables E, G, M, Q, and U.

IT 648577-67-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzimidazoles and imidazopyridines having affinity for melanocortin (MC), in particular MC4, receptors)
RN 648577-67-3 HCAPLUS
CN 1H-Benzimidazole-6-carboxamide, N,N-bis(3-methylbutyl)-1-[3-(1-piperidinyl)propyl]-2-[[4-(1-piperidinylsulfonyl)phenyl]amino]- (9CI) (CA INDEX NAME)



Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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